Introduction
1. INTRODUCTION

Heterocyclic compounds occur widely in nature and in a variety of non-naturally occurring compounds. These compounds are very essential in many ways for life. They play an important role in metabolic activities of all living cells. Contemporary organic chemistry is paying more and more attention to the development of methods for the synthesis of condensed heterocyclic structures. The interest in such compounds is due to the prospects of seeking new biologically active substances, since such molecules contain pharmacophoric fragments. Very frequent mechanistic investigations of these heterocyclic compounds provide aids to understand the chemistry of these compounds. The interesting properties possessed by these compounds, the brilliant colours of flowers and fruits and poisonous or healing properties of so many plants and herbs have attracted many chemists towards their study from which have come important findings. Such findings gave significant contributions to other fields like genetics, agriculture and medicine.

Of the heterocyclic compounds, the oxygen, sulphur and nitrogen heterocycles constitute very important group of compounds. Sulphur containing heterocycles represent an important group of sulphur compounds that are promising for use in practical applications. For instance thiacycloalkanes are starting materials for the synthesis of physiologically active substances; unsubstituted thiolane is used as an odorant for ages; thiophenes can be used as physiologically active substances, dyes and oil additives. The synthesis of quinolines and their derivatives has been of considerable interest because a large number of natural products and drugs contain this heterocyclic unit (Morimoto et al, 1991; Isobe et al, 1992; Markees et al, 1970; Alhaider et al, 1985; Campbell et al, 1988). Quinoline-4-carboxylic acids and their analogs have a wide variety of medicinal applications including antitumour, antiviral and antibacterial activities (David, 1987; Yu et al, 2001). 2-(4′-Bromophenyl)-quinoline-4-carboxylic acid selectively inhibited C. albicans. Prolyl-tRNA synthetase and 2-phenylquinoline-4-carboxamides are used as analgesic, tranquillizer, antitumour, and antitubercular agents (Kar, 1983; Dubroeucq, 1984; Atwell et al, 1984; Medvecky et al, 1991). Thieno quinolines form a class of hetero aromatics in which the thiophene ring is fused to the quinoline nucleus. There are several reports (Makitsuno, 1973, Makisumi, 1969; 1970; 1974, Makikado, 1973, Sarithadevi et al, 1993) on the pharmaceutical and biological activity of these compounds.

Dihydrothieno quinolines are heterocyclic ring systems of considerable interest due to several biological and pharmaceutical activities associated with this scaffold: Some analogues have been found to act as effective pharmaceutical and biological agents.
Consequently, it was decided to try to corner the interest to dihydrothienoquinolines and the precursors required for its synthesis - quinolone, chloroquinolines and thione.

Heterocyclic compounds can be synthesized in a number of ways. The most conventional and common method is refluxing the reactants. In most of the reactions, the process consumes lot of time. Several reactions end up in impure products. It is normally a tedious job for a researcher to purify a compound. Also many reactions require use of large amounts of solvents. Though it is a common practice to run organic reactions in solvent media, the chemist’s concern to minimize the environmental pollution caused by solvents and also their academic interest in solid-solid reactions have led them in recent times to develop methodologies for solvent-free reactions with considerable success (Nagendrappa, 2002). Solvents like benzene, chloroform, acetonitrile, CCl₄, allyl alcohol, CS₂, diazomethane, DMF, DMSO, dioxan etc. are toxic and harmful. Recently in U.S.A the use of benzene has been banned (Antus et al, 2004). Hence chemists, search for methods which require use of lesser amounts of solvents. While microwaves are both financially and energetically expensive to produce, the efficiency with which they can be used makes them an attractive ‘green’ alternative to other forms of heating. Moreover, in recent years there has been a drive within the chemical industry to reduce both the production of waste products and the use of solvents. Waste products equate with wasted resources, and solvents can be toxic, flammable and expensive to dispose off. Microwave chemistry provides a cleaner alternative, by exploiting the ability of microwaves to heat the reactants directly.

Recently much focus is on such improvised methods of synthesis like: use of microwave irradiation, ultrasound (sonochemistry), yeast and solid support aided reactions. Reviewing on the foresaid matter, a search made for a suitable methodology to adopt, for synthesis of heterocyclic compounds, narrowed to microwave synthesis owing to its user-friendly nature. Practical applications of microwave synthesis would thus be reviewed extensively and exploited in the present work.

1.1 Microwave Synthesis

Recently, a new technique that is set to revolutionize synthesis has moved to the forefront of chemical research: microwave-assisted organic synthesis (MAOS). It represents one of the important dimensions of modern chemistry.

Microwave technology has been used in chemistry since the late 1970’s, but it has been implemented in organic synthesis only since the mid-1980’s. The slow uptake of the technology has been attributed to its initial lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating.
However, since the late 1990’s, the number of publications related to MAOS has increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use quick bursts of microwave energy to heat and drive chemical reactions. Agrochemical and biotechnology companies are already using MAOS as a forefront methodology for library synthesis and lead optimization as they have realized the ability of this enabling technology to speed chemical reactions.

In the last few years there has been an increased interest in the use of microwave heating in organic synthesis (Abramovitch, 1991; Mingos and Baghurst, 1990; 1992; Laurent et al, 1992). The use of such non-conventional reaction conditions reveals several features like: a short reaction time compared to conventional heating, ease of work-up after a reaction and reduction in the usual thermal degradation and better selectivity (Abrmovitch,1991;Bose et al, 1991;Gedye et al , 1988; Gigure et al, 1986;Majetich and Hicks, 1995). Reactions under dry conditions were originally developed in the late 1980’s (Smith,1992). Synthesis without solvents under microwave irradiation offers several advantages (Bram et al,1992). The absence of solvent reduces the risk of explosions when the reaction takes place in a closed vessel in an oven. Specially, microwave accelerated solvent-free reactions have received much attention because of minimization of safety problems (Varma, 2001;Loupy et al,1998). Moreover, aprotic dipolar solvents with high boiling points are expensive and difficult to remove from the reaction mixtures.

The basis of this fast developing synthetic technique is the empirical observation that some organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating (Varma,1999). Although different hypotheses have been proposed to account for the effect of microwave on organic reactions (Pagnotta et al, 1993), the reason for the dramatic acceleration effect is thought to be instantaneous super heating of the reaction medium. Regardless of the exact origin of the microwave effect, it is found to be extremely efficient and applicable to a very broad range of practical syntheses (Villemin and Caillot, 2001). Parallel to developments in Diversity Oriented Synthesis (DOS) (Schreiber, 1998; Lee et al, 2000; Weber, 2000) and combinatorial chemistry, microwave enhanced synthesis has attracted substantial attention in recent years, enabling many organic reactions to proceed much faster and with higher yields than when conventional heating is employed (Kappe et al, 1999). Most reaction rates are accelerated by increasing the reaction temperature. For every 10°C increase in temperature, the rate is approximately doubled. The maximum temperature of a reaction is usually the boiling point of the solvent. But in a closed microwave vessel, the temperature of the mixture can be
raised further, so the reaction rate increases accordingly. They result from material-wave interactions leading to thermal effects and specific effects resulting from variations in activation parameters, enhancements in molecular impacts and possibly localized microscopic temperatures.

Microwave heating allows substantially improved productivity of many chemical processes with reduced formation of by-products caused by overheating. Microwave irradiation produces efficient internal heating resulting in even heating throughout the sample, as compared with the wall heat transfer that occurs when an oil bath is applied as an energy source. Consequently, the tendency for the initiation of boiling is reduced and superheating above the boiling point of the solvent. Not only are microwaves sometimes able to reduce chemical reaction times from hours to minutes, but they are also known to reduce side reactions, increase yields and improve reproducibility (Loupy, 2002; Hayes, 2002). Using only a minimal amount of solvent, the reactants are absorbed into a sponge-like support material (clays, alumina, zeolite etc). The reactants are then heated directly with microwaves to generate the products, which are then extracted, again with minimal solvent. Because microwave heating is essentially uniform throughout the material, there is no time lost waiting for thermal conduction to heat the sample and consequently, reaction times are often measured in minutes or even seconds.

Utilizing microwave irradiation, several reactions of synthetic importance such as alkylation (Bram and Loupy, 1990), condensation (Gigurere et al, 1986), halogenation (Kad et al, 1997) and oxidation (Varma et al, 1997) have been reported in literature recently.

The advantages of microwave synthesis when compared to the conventional techniques, summed up are:

- wide range of chemical modification
- able to be used with variety of solvents
- remarkable stability to chemical agents
- simple handling of samples
- drastic reduction in reaction time
- better selectivity and stability of the reaction product and sample enrichment
- green method of synthesis

_Henceforth it has been aimed to exploit the use of microwave technology._

The utility of microwave in heterocyclic synthesis is now receiving considerable attention (Caddick, 1995; Loupy et al, 1998; Perreux and Loupy, 2001; Lidstrom et al, 2001) and, although thiones, quinolones and chloroquinolines are extensively utilized as
precursors for the synthesis of heteroaromatics like thienoquinolines, the microwave enhanced synthesis of the foresaid precursors has not been previously investigated. The methods reported from other laboratories for the synthesis of 2,3-dihydrothienoquinolines are a few in number and they have been mostly tried only on the parent compound. **The plethora of synthetic methodology reported for these potentially biologically important heterocyclics- dihydrothienoquinolines and the precursors required for its synthesis, and the paucity of microwave reactions of these compounds was adequate motivation for the present work.**

*Another area of organic synthesis which snatched interest and attention is solid-support promoted synthesis.* Several workers have successfully carried out reactions which were difficult to take place, by the use of solid supports. Solid supports are based on chemical mode of core surface. These new supports have shown a large list of chemical functionalisations and can be used for different applications like chemical scavengers, enzymes, catalysts etc.

### 1.1.1 Microwave and Solid Supports

Reactions using reagents or reactants on insoluble inorganic supports have stimulated considerable interest among synthetic chemists recently. There has been an increasing use of inorganic solid supports as catalysts for many years (Villemin and Ricard, 1984; Cabello et al., 1984). Advantages frequently claimed in favour of supported reagents compared with their homogenous counterparts are ease of set-up and work-up, mild experimental conditions, rapid reactions and gain in yield and/or selectivity. It has also been demonstrated that attempts to carry out the same reactions with unsupported reagents frequently either fail or result in the formation of a mixture of products (Ranu and Bhar, 1992).

Organic reactions on solid supports (Mckillop and Young, 1979; Varma et al., 1993; Varma and Saini, 1997; Varma et al., 1997; Varma and Meshram, 1997) and those assisted by microwaves (Villemin and Benalloum, 1991; Whittaker and Mingos, 1994; Caddick, 1995; Bose et al., 1997; Varma, 1997) especially under solvent-free condition have attracted ease of manipulation. Since only the polar reactants adsorbed on the surface of the solid support absorb microwaves, a variety of reagents supported on such surfaces can be utilized for the enhancement of organic reactions using an unmodified microwave oven. During microwave induction of reactions under dry conditions, the reactants adsorbed on the surface of alumina, silica gel, clay and others absorb the microwaves whereas the support does not, nor does it restrict the transmission of
microwaves. Consequently, such supported reagents efficiently induce reactions under safe and simple conditions with domestic microwave ovens instead of specialized expensive commercial microwave systems. Many microwave reactions have been found to perform well with supported reagents on recyclable inorganic oxides or clays (i.e. silica, alumina, bentonite and montmorillonite) (Varma, 2002).

Inorganic oxides (alumina, silica) and acidic clays (montmorillonite K10 or KSF) have been used as carriers in microwave assisted solventless organic reactions (Villemin, 1985; Mingos, 1992; Petit et al, 1992). The strategy of microwave activated synthesis on solid inorganic supports (Gutierrez et al, 1989; Ben Alloum et al, 1989) seems to be the most efficient technology. Acidic and basic solid mineral oxides such as silica gel, alumina etc., act both as catalysts and supports (Bram et al, 1989).

The number of publications using solid-supported organic synthesis has exploded as a result of its employment in the field of combinatorial chemistry. Several recent reviews list an ever widening array of new reactions that have been run on solid-supports (Kresge et al, 1992; Beck and Vartuli, 1996). Unfortunately, the application of reactions requiring high temperatures has received little or no attention mainly because many supports decompose at elevated temperatures. Clearly, there are many reactions that require elevated temperatures and, if translated to a solid support, they could dramatically extend the number of novel scaffolds available for combinatorial library synthesis (Irving et al, 1998).

The present investigation was thus undertaken with the confident expectation that microwave technology aided by solid supports-alumina, montmorillonite clay, bentonite, silica gel, dowex and amberlite could be conveniently exploited for the production of dihydrothienoquinolines and its precursors- quinolones, chloroquinolines and thiones.

1.2 Electrochemical Techniques and Biological Activity of Heterocyclics

The biological electron transfer reactions and the electrochemical electron transfer reactions have many things in common. Electrochemical and biological electron transfer or oxidation–reduction reaction, both involve essentially heterogenous electron transfer processes and occur at electrode/electrolyte interface or at membrane solution interface. The specific orientation of the substrate molecule towards the active site of the enzyme, in the case of biological reactions and towards the electrode in the case of electrochemical reactions is a precondition for the reaction to occur (Ramesh and Muralidharan, 1985). Explanations based on electrochemistry have played an important role in interpreting the biological phenomena. However, presently the investigations of biological problems have not set to use, the sophistication of the electrochemical technique and methodology and the
perceptive studies possible for biologically important compounds. Thus electrochemical studies, in conjunction with all the other experimental and theoretical tools of chemistry, should be able to contribute significantly to the ultimate understanding of many biological electron transfer reactions (Aszent Gyorzi, 1960).

The electro-chemical characteristics of carbonyl compounds are historically of interest. Therefore, ketones (Bogdanovsty et al., 2002), α-keto acids (Ohmori et al., 1977), aldehydes (Vesely et al., 1947 and Kumar et al., 1962) and di and tricarbonyl molecules (Fleury et al., 1975; Ono et al., 1958) and many other carbonyl compounds have been frequently studied. Cathodic reduction of alpha halo carbonyl substrates has been demonstrated to be a useful procedure to synthesize heterocyclic compounds (Barba and Batanero, 1993; Barba and Feunte, 1996; Batanero et al., 2001; Batanero and Barba, 2001).

During recent years a number of methods have been developed for the measurement of electrode reaction kinetics. In one sense, some of these determine electrode reversibility indirectly by measuring the apparent standard rate constant for electron transfer from only cathodic (or anodic polarization). In a few cases both cathodic and anodic polarization gives consistent results. Many of the relaxation techniques developed for fast reactions have the disadvantage that small amplitude perturbations are used, and consequently differences or changes in mechanisms are not easily detected. A method which overcomes this disadvantage and at the same time gives a direct estimate of reversibility is cyclic triangular wave voltammetry. Thus the presence of homogenous reactions in the mechanism is readily detected, and interpretation of result usually is simple. A direct estimate of electrode reversibility is provided, because the potentials at which oxidation and reduction occur are observed directly.

Many quinolones, substituted quinolines and thiones are well known for their biological activity. Quinolin-2-one derivatives have received considerable attention in organic chemistry due to their use as anti-inflammatories, antihypertensives, and analgesic agents or in the preparation of antipsychotic agents. 3-halo-2(IH)-quinolinones have been used as cardiac stimulants and as herbicides. The redox characteristics of such biological substances may provide valuable information about the redox behaviour in living systems.

Electrochemical reduction of thiocarbonyl compounds has received only very little attention (Simonet et al., 1993; Yasui et al., 1982), probably due to the limited solubility as well as their stability in inorganic solvents. In general stable thiones are more easily reduced than the corresponding carbonyl structures, and stable aromatic thioketones, such as
thiobenzophenone upon one electron reduction, produce a highly stable anion radical, which has been demonstrated to play the role of a nucleophile towards a variety of alkylating agents.

*In view of the biological activity of quinolones, quinolines and thiones and the usefulness of electrochemical techniques in studying biological molecules, the present study is also aimed at employing the technique of cyclic voltammetry and analyzing the electrode reactions at glassy carbon electrode.*

### 1.3 Electro Organic Chemistry

The wide range of research activities in the field of electroorganic chemistry is reflected in large number of publications (Brockman, 1926; Swan, 1936; Kolthoff and Lingane, 1952; Allen, 1958; Popp and Schultz, 1962; Weinberg and Weinberg, 1968; Sasaki and Newby, 1969; Brown and Harrison, 1969; Conway and Vijn, 1967; Zuman, 1967; Adams, 1969; Bard, 1973). Electroorganic reactions may be conveniently classified into conversion, substitution, addition, elimination, cyclization, coupling, cleavage and electron transfer reactions on the basis of products formed (Weinberg, 1975). Generally, the use of an electrochemical method should be considered if a known chemical procedure is too laborious, affords too low yields, uses expensive starting materials and/or cannot be easily adopted on a large scale. It is under such circumstances that electrolytic methods have their main advantages. They often make use of cheap starting materials, provide short-cuts in multi-stage reaction schemes and give reasonable yields by stepless regulation of the oxidizing or reducing power of the electrode. Moreover, the medium employed should be chemically inert so that further chemical reactions of reactive products can be avoided (Harborne, 1972). It should also be added that electrochemical reactions often lead to products of unusual stereochemistry as compared to homogenous reactions. Electrochemical methods do come into play in the absence of any known chemical procedure for the preparation of a desired compound (Prabavathi, 1993).

#### 1.3.1 Cyclic Voltammetry (CV)

One of the workhorses of electrochemical measurements is cyclic voltammetry, an electrochemical technique that is capable of providing a wealth of information about an electrochemical system. It is one of the electro analytical techniques utilized by analytical and synthetic chemists alike and is important in investigating the kinetics and mechanisms of redox reactions (Kissinger 1983; Mabbott, 1983). Cyclic voltammetry is often the first experiment performed in an electrochemical study of a compound on an electrode surface. The effectiveness of CV results from its capability for rapidly observing the redox behavior
over a wide potential range. The resulting voltammogram is analogous to a conventional spectrum in that it conveys information as a function of an energy scan. Information related to analyte concentration, electrode reaction kinetics and diffusion contributions are all contained in a cyclic voltammogram.

In cyclic voltammetry, the potential applied to an electrode, designated as the working electrode, is scanned in a linear fashion between two potential values. The working electrode serves as the surface where the electron transfer of the redox reaction occurs. The redox reaction occurs within the potential range defined by the two chosen potential values, and the potential at which the reduction or oxidation takes place provides qualitative information about the analyte of interest. The application of an electrical potential to a working electrode makes the surface, an electrochemical reductant or oxidant, depending on the applied potential. As the applied potential becomes more negative, the electrode becomes a better reducing agent. Conversely, as the applied potential becomes more positive, the electrode becomes a better oxidizing agent.

Applications of CV have been extended to almost every aspect of chemistry. Few include:

1. Determination of
   - capacitance of electrochemical interfaces
   - formed potential
   - diffusion coefficient
   - electrochemistry of complexes

2. Investigating the effects of electrode contamination on cyclic voltammetry

3. Quantitative diagnosis of the homogenous chemical reactions that are coupled to the electrode surface reaction.

4. Determining the mechanism and rate of the chemical reaction based on a linear potential waveform. The rate of change of potential with time is referred to as the scan rate. CV provides the capability for generating a species during the forward scan and then probing its fate with the reverse scan and subsequent cycles, all in a matter of seconds or less. In addition the time scale of the experiment is adjustable over several orders of magnitude by changing the potential scan rate, enabling some assessment of the rate of various reactions.

5. Acquiring qualitative information about electrochemical reactions.

Classical cyclic voltammetry can be used to monitor electro-generated transient compounds formed from tens of seconds to the sub millisecond domain. The technique of redox catalysis developed by Saveant and co-workers has greatly extended the range of time
scales available to voltammetric measurements. (Saveant, 1985; Andrieux and Saveant, 1986). However, recent developments in the miniaturization of electrodes and experimental procedure have led to a significant increase in the time resolution of cyclic voltammetry. Voltammograms with interpretable data have been obtained at the sub microsecond time scale with the use of scan rates in the millions of volts per second range (Wipf and Wightman, 1988; Wipf et al, 1988; Andrieux et al, 1988; Amatore et al, 1987). Cyclic voltammetry, therefore, can now be used to directly monitor reactions over a time scale of 8 orders of magnitude.

The real power of the technique lies in its ability to investigate mechanisms and potential of electrode reactions. In view of the foresaid factors the present work is aimed at utilizing cyclic voltammetry in studying the behaviour of few heterocyclic compounds.

1.3.1.1. Significance of Solvents and Supporting Electrolytes in Cyclic Voltammetry

The peak potential values of compounds vary with the nature of the solvent used. Marked differences are even noted when the solvents are protic or aprotic. There is no universal solvent and in general, the solvent whose merits outweigh its disadvantages for a particular application is chosen. The most desirable properties of a solvent are its electrochemical inertness, electrochemical conductivity, good solvent power, chemical inertness and convenient liquid range. The solvent should not undergo any electrochemical reaction over the range of working potentials from highly positive to highly negative values. The cyclic voltammetric behaviour of hydroxy flavones in DMF was found to be more negative than in aqueous medium (Prabhavathi, 1993). In order to optimize conditions for an electrode reaction, one must consider how it’s chemical and electrochemical features might be affected by the solvent or electrolyte. In order to facilitate smooth passage of an electrical current, the solvent system should have low electrical resistance and hence moderately a high dielectric constant (Delahay and Tobias, 1961).

Henceforth the present study is intended to analyze the difference in cyclic voltammetric behaviour of few heterocycles with variation in solvent – DMF, acetonitrile (AN), THF and methanol (MeOH). All these solvents have satisfactory dielectric constant and are more commonly used in cyclic voltammetry experiments.

As supporting electrolytes the tetra alkyl ammonium salts have continued to be useful. Their range has been found to be dependent upon their purity. It has been suggested that catalytic hydrogen waves are responsible for the wave observed with these salts and not the reduction of the cation. High solubility and low solution resistance make them best choice of electrolyte.
Contemplating on the importance of electro-organic synthesis and cyclic voltammetry, an attempt has been made in the present work to exploit these fields in the study of few heterocyclic compounds using various solvents such as acetonitrile, methanol, DMF and THF and under various pH conditions using BR buffer in the presence of tetra butyl ammonium bromide as supporting electrolyte.

1.4 Significance of Log P and Activity Studies

Synthetic organic compounds find wide application in various fields like medicine, agriculture etc. Chemistry is just one discipline in the interdisciplinary endeavour, involving drug discovery and development. Medicinal chemistry is at the forefront of innovation, blending synthetic chemistry, molecular modeling, computational biology, structural genomics and pharmacology to discover and design new drugs, and investigate their interaction at the molecular, cellular and whole-animal level.

The intersection of chemistry and pharmacy is involved in designing and developing pharmaceutical drugs. Knowledge of heterocyclic chemistry is useful in biosynthesis and drug metabolism as well. A large number of heterocyclic compounds are essential to life. Various compounds such as alkaloids, antibiotics, essential amino acids, vitamins, haemoglobin, hormones and many synthetic drugs contain heterocyclic ring systems. Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents.

Quinoline compounds are such heterocyclic compounds possessing a wide range of antibacterial, antifungal and antimutagenic properties. QSAR studies have proved the pharmaceutical and biological importance of many quinoline compounds. (Hayes et al, 2002). A number of alkaloids containing quinoline nucleus are well known and many of them function as therapeutic agents. Quinine has been a standard drug for the treatment of malaria for centuries. The recent discovery of thiophene compounds in fungi and higher plants has awakened the interest of the natural product chemist in the chemistry of thiophenes. The broad application spectrum and in vivo efficiency of quinolone antibacterials (Wise et al, 1983), thiadiazoles (Ashour et al, 1990) and oxadiazoles (Dort and Counsel, 1987) have generated much enthusiasm in the medical community and prompted extensive research in the pharmaceutical industry as well. Substituted quinolones have been prepared by nucleophilic substitution reactions using heterocyclic groups like piperazinyl, pyrrole etc. under basic conditions (Gonzalez, CA 120).

Dihydrothieno quinolines, vinyl-2-quinolones, vinyl-2- chloro quinolines and 3-vinyl-quinolin-2-thiones are heterocyclic ring systems of considerable interest due to several
biological activities associated with these compounds. Earlier workers have prepared several C4 substituted as well as C4 unsubstituted -3-vinyl-2-quinolones and exploited them for the synthesis of furo-, thieno-, selenolo-, tellurolo- and pyrroloquinolines (Balasubramanian, 1989). The chemistry of thienoquinolines has been exploited to a limited degree (Sarithadevi, 1993). Interest in these systems arises from the reported pharmacological properties of isomeric quinolines. For example several derivatives of thieno (3,2-c)quinolines were reported to be useful as antipyretic (Makisumi,1974;1969;1970;Makitsuno,1973), analgesic (Makisumi, 1969; 1970; 1974) anti-inflammatory and sedative agents. Derivatives of thieno – (3,2-c) quinolines were also reported to be useful as herbicides and insecticides (Makikado,1973). Thieno (3,4 - b) quinoline, an o-quinonoidal heterocycle is of interest both for the theoretical reasons compared with its conjugate analogues and as a synthon in Diel’s – Alder reactions for the preparation of other condensed heterocycles (Sarithadevi et al, 1993). It is expected that quinolines would possess interesting pharmacological properties which might prove to be of value in human and animal health.

Owing to the significant biological and pharmacological activity of the organic compounds as seen from literature hunt, it was felt essential to explore the importance of dihydrothieno quinolines, vinyl-2-quinolones, vinyl-2- chloro quinolines and vinyl-2-thiones. The drug likeness of these compounds has been tested theoretically first and the antibacterial, antifungal, antimutagenic activity has been tested for the synthesized compounds by suitable laboratory tests.

1.4.1 Significance of Log P

A series of features commonly found in orally active drugs has been identified and referred to as Lipinski's rule of five and can be used as a rule of thumb to indicate whether a molecule is likely to be orally bio-available (bioactive). The "rule of five" is so called because most of the features start with the number five.

In general, an orally active drug has:

- not more than 5 hydrogen bond donors (OH and NH groups)
- not more than 10 hydrogen bond acceptors (notably N and O)
- a molecular weight under 500
- a log P value under 5

Lipinski's work has since been extended to include properties such as the number of rings and rotatable bonds. Molecules violating more than one of these rules may have problems with bioavailability (Lipinski, 1997). Christopher Lipinski's rule-of-five analysis helped to raise awareness about properties and structural features that make molecules more
or less drug-like. The guidelines were quickly adopted by the pharmaceutical industry as it helped apply ADME considerations early in preclinical development and could help avoid costly late-stage preclinical and clinical failures. It has been a critical filter for drug development programs, since its publication in 1997. Drug discovery programs worldwide use the rule as a filter in high-throughput screening libraries.

One important descriptor in the rule is log P. LogP is a measure of differential solubility of a compound in two solvents. The log ratio of the concentrations of the solute in the solvent is called Log P or the partition coefficient. The most well-known of these partition coefficients is the one based on the solvents - Octanol and Water. In the context of drug-like substances, hydrophobicity is related to absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism and toxicity. Lipophilicity is one of the parameter of chemical substances, which influence the biological activity of drugs. It is a prime parameter in describing both pharmacodynamic and pharmacokinetic aspects of drug action. Lipophilicity is defined by the partitioning of a compound between a non-aqueous and an aqueous phase. It affects numerous properties of drugs including solubility, permeability, metabolism, binding and distribution (Oile et al., 1986).

Lipophilicity is a measure of the degree to which a given molecule prefers hydrophobic nonpolar environments to water. This quantity has been measured experimentally for a wide range of organic compounds (Reynolds and Best, 1998):

$$\log P = \log \left( \frac{[S]_{\text{org}}}{[S]_{\text{aq}}} \right)$$

The partition coefficient for octanol–water (log Pow) has become the preferred measure for lipophilicity in the development of biologically active molecules, in which transport across biological membranes is often critical (Carrupt et al., 1997; Hansch and Leo, 1979; 1995; Martin, 1978) Since the concept of lipophilicity is so important in chemistry, many schemes have been developed to estimate this property as expressed by the partition coefficient log P. Some of the best known methods, such as Leo’s CLOGP program (Leo, Daylight Chemical Information Systems), rely upon summing group contributions of structural fragments to calculate log P directly from the two–dimensional structure of a molecule. Methods for calculating log P were surveyed in a 1997 review. (Carrupt, Boyd, 1997). Since the work of Meyer and Overton a century ago, (Meyer, 1899; Overton, 1899; Peruzzo et al, 2003) lipophilicity has been recognized as a meaningful parameter in structure–activity relationship studies, and the epoch–making contributions of Hansch (Hansch et al, 1962) has become the single most informative and successful physico-
chemical property in medicinal chemistry (Hansch and Leo, 1979; Helmer et al, 1968; Rekker, 1977).

A survey of literature shows that several studies have been focused on the determination of log P values. For several dimers, lipophilicity was considered a useful parameter in bioactivity. Recently, reports have appeared (Marica Medi, 2004) on high HIV integrase inhibitory potency of certain coumarin dimers’ analogues. The widespread application of lipophilicity to drug design explains the need for quick procedures to quantify molecular lipophilicity, particularly at the screening level. Log P has also become a key parameter in studies of the environmental fate of chemicals.

*Giving consideration to the significance of log P, a spotlight is made on the theoretical determination of log P and other molecular properties like refractivity, polarisability, polar surface area, log S, molecular volume, drug likeness and number of rotatable bonds, using computer programs.*

1.4.2 Activity Studies

One method of measuring the effectiveness of a chemical agent is to determine its zone of inhibition. The agar diffusion method is a popular method in determining the zone of inhibition. Of fairly greater clinical relevance is the minimum concentration that will inhibit the growth of a particular microbe. The basic quantitative measures of the *in vitro* activity of antibiotics are the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC). The MIC is the lowest concentration of the antibiotic that results in inhibition of visible growth (i.e. colonies on a plate or turbidity in broth culture) under standard conditions. The MBC is the lowest concentration of the antibiotic that kills 99.9% of the original inoculum in a given time. The minimal inhibitory concentration (MIC) gives an indication of the dosage of antibiotic that should be effective in controlling an infection. By knowing the MIC and the levels of antibiotic that may be achieved in body fluids, the physician can select the appropriate antibiotic, dose schedule and route of administration.

*The disc method has been employed in the present work for determination of antibacterial activity, streak plate isolation method for determination of antifungal activity, and agar diffusion method for determination of MIC’s and Ames Salmonella microsome assay for determining the antimutagenic effect of the foresaid compounds.*
1.5. Objectives of the Thesis

The present work has been carried out in 3 phases.

**Phase I**
Process improvement strategy in the synthesis of dihydro [2, 3-b] thieno quinolines, 3-vinyl-2-quinolones, 3-vinyl-2-chloro quinolines and 3-vinyl quinoline-2-thiones via microwave enhanced synthesis aided by solid supports.

**Phase II**
Electrochemical investigation of the reduction behaviour of 3-vinyl-2-quinolones, 3-vinyl-2-chloro quinolines and 3-vinyl quinoline-2-thiones via cyclic voltammetry

**Phase III**
Activity studies of the foresaid compounds both theoretically employing computer programs and experimentally by suitable laboratory tests.

**In this thesis are described**
the investigation efforts spent towards the

- realization of the microwave enhanced and solid support aided synthesis of dihydrothienoquinolines, 3-vinyl-2-quinolones, 3-vinyl-2-chloro quinolines and 3-vinyl quinoline-2-thiones
- realization of electro-reduction studies of the foresaid compounds
- realization of the pharmaceutical and biological activity of the foresaid compounds
- the review material pertinent to them
- the experimental details of the three phases of work carried out
- the results obtained
- and the alluring conclusions such a study led to

The present work has been carried out with the following broad objectives in view:

i. To carry out an extensive review pertinent to microwave reactions, solid support enhanced reactions of heterocyclic compounds with particular reference to sulphur and nitrogen heterocycles, cyclic voltammetric studies of organic compounds, pharmacological importance of heterocyclic compounds and lipophilicity studies of organic compounds.

ii. To review the different methods of synthesis of dihydro thienoquinolines.

iii. To employ microwave technology as a process improvement strategy in the synthesis of 4-substituted -3- vinyl quinoline-2(1H) ones, 2-chloro-3-vinyl quinolines, 3-vinyl quinoline-2(1H)-thiones and their corresponding dihydrothienoquinolines.
iv. To employ microwave technology aided by solid supports—alumina, montmorillonite clay, bentonite, silica gel, dowex and amberlite, as a process improvement strategy in the synthesis of 2-chloro-4-methyl-3-vinyl quinolines, 2-chloro-4-phenyl-3-vinyl quinolines, 2,6-dichloro-4-phenyl-3-vinyl quinolines, 6-nitro-2-chloro-4-phenyl-3-vinyl quinolines, 4-methyl-3-vinyl quinoline-2(1H)-thiones, 6-chloro-4-phenyl-3-vinyl quinoline-2(1H)-thiones and 4-phenyl-3-vinyl quinoline-2(1H)-thiones.

v. To make a comparison of the conventional method of synthesis and process improvement method—microwave synthesis with and without solid support, in terms of yield of product and time of reaction.

vi. To pry into the mechanism of conversion of 4-cyano-3-vinyl quinoline-2(1H)-thiones to the corresponding dihydro derivative in the presence of bromine in chloroform and a requisite amount of triethylamine.

vii. To carry out a methodical cyclic voltammetric investigation of the peak potential values of 4-methyl/phenyl-3-vinyl quinoline-2(1H)-one (MVQ/PVQ), 2-chloro-4-methyl/phenyl-3-vinyl quinoline (CMVQ/CPVQ), 4-methyl/phenyl-3-vinyl quinoline-2(1H)-thione (TMVQ/TPVQ), 6-chloro-4-phenyl-3-vinyl quinoline-2(1H)-one (ACBP) and 6-nitro-4-phenyl-3-vinyl quinoline-2(1H)-one (ANBP) in tetrahydrofuran (THF) with tetra butyl ammonium bromide (TBAB) as supporting electrolyte at different pH with Britton–Robinson buffer at glassy carbon electrode. The effect of scan rate and concentration of compounds would be studied at different pH (2, 4, 6, 8 and 10).

viii. To investigate the solvent effect a systematic cyclic voltammetric investigation of the peak potential values of one representative compound-MVQ would be carried out in different solvents—THF, dimethyl formamide (DMF), methanol and acetonitrile (AN) in the presence of supporting electrolyte—tetra butyl ammonium bromide (TBAB). The effect of scan rate and concentration of compounds would be studied at different pH (2, 4, 6, 8 and 10).

ix. To carry out a meticulous cyclic voltammetric investigation of the effect of solvent (protic and aprotic), scan rate, pH, concentration and substituent effect on the electro reduction behaviour of the foresaid compounds.

x. To arrive at the mechanism of the electrochemical behaviour, obtained for the compounds under study.

xi. To create Hyperchem built files for the compounds under study, for the determination of Quantitative Structure Activity Relationship Properties.
To theoretically determine the log P and other molecular properties like refractivity, polarisability, polar surface area, log S, molecular volume, drug likeness and number of rotatable bonds, using computer programs- HyperChem 7.0, XLOGP, KowWin, CLOGP, ALOGPS 2.1, IA logP, miLogP using Molinspiration and MolSoft. The drug likeness would be calculated using Molinspiration and MolSoft programs.

To compare the zone of inhibition of the synthesized compounds – MVQ, PVQ, CMVQ, CPVQ, TMVQ, TPVQ, ACBP, ANBP, DMVQ against 6 bacteria - *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and proteus species by disc method.

To arrive at the minimum inhibitory concentration of PVQ, CPVQ and TPVQ for antifungal activity by streak plate isolation method.

To compare the antimutagenic activity of few synthesized compounds against *Salmonella typhimurium* (TA 98)